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Precapillary Pulmonary Hypertension and Sleep-Disordered Breathing: Is There a Link?

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Keywords
Pulmonary hypertension · Sleep-related breathing disorders · Sleep apnea · Cheyne-Stokes respiration · Heart failure

Abstract
Among patients with sleep apnea the reported prevalence of precapillary pulmonary hypertension (PH) has varied largely, depending on patient selection, disease definition, and associated conditions, in particular chronic pulmonary disease. However, in the absence of comorbidities, PH seems to be rare in patients with sleep apnea. Conversely, sleep-related breathing disorders have been commonly found in patients with PH and they have been associated with an impaired quality of life. Since sleep-related breathing disorders may affect the pulmonary circulation and vice versa, patients with sleep-related breathing disorders should be evaluated for risk factors, symptoms and clinical signs of PH and right ventricular heart failure and patients with PH should be evaluated for sleep apnea. Therapeutic options for patients with sleep apnea and PH may include supplemental oxygen, drugs and positive pressure ventilation. Both nocturnal oxygen administration and acetazolamide have been shown to improve sleep apnea in patients with PH. In addition, oxygen therapy also improved exercise performance. Further studies are needed to corroborate the efficacy of these and other treatments.

Introduction

Precapillary pulmonary hypertension (PH) and right ventricular heart failure occur in certain patients with sustained hypoxemia due to obesity hypoventilation syndrome [1] and severe sleep-related hypoventilation, and in high-altitude residents suffering from chronic mountain sickness [2]. Whether precapillary PH may also develop as a consequence of intermittent hypoxemia during sleep such as in patients with obstructive sleep apnea (OSA) is controversial. While up to 50% of adults in Western countries are estimated to be affected by various severities of OSA [3–5], only a minor fraction of these individuals are considered to suffer from precapillary PH [6]. Conversely, among patients with precapillary PH, either pulmonary arterial or chronic thromboembolic (WHO classes I or IV), a high prevalence of central sleep

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apnea (CSA) and OSA has been observed suggesting a pathophysiologic link [7].

In patients with postcapillary PH due to severe left ventricular heart failure (WHO class II), Cheyne-Stokes respiration/CSA (CSR/CSA) is quite common and this association is considered to indicate a poor prognosis. Compared to sleep-disordered breathing (SDB) in the context of left ventricular failure, which has been the topic of a review article in this journal [8], SDB in association with precapillary PH has gained much less attention. Therefore, the aim of the current review is to analyze the literature on this association with a particular focus on the pathophysiologic mechanisms linking SDB and precapillary PH. We further review the prevalence and importance of precapillary PH in patients with SDB and of SDB in patients with PH, and we analyze the prognostic and therapeutic implications of SDB in association with PH.

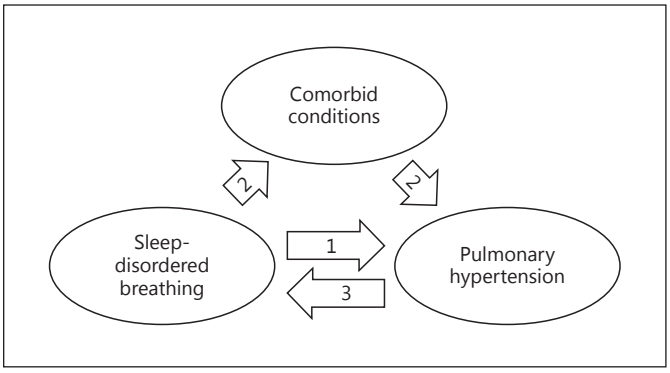

Fig. 1. The interaction between sleep-disordered breathing and precapillary pulmonary hypertension may be mutually mediated by direct effects (arrows labelled 1 and 3) or via comorbid conditions (arrow 2), in particular, chronic respiratory diseases such as chronic obstructive pulmonary disease or obesity hypoventilation syndrome.

Mechanisms Linking Precapillary PH and SDB

During normal sleep, there is a fall in heart rate and systemic arterial blood pressure with lowest values in deep non-rapid eye movement (NREM) sleep [9]. In rapid eye movement (REM) sleep, pulmonary arterial pressure (PAP) becomes unstable and increases compared to NREM sleep [10]. However, no relevant differences in PAP were seen between the first and the second half of a night in healthy individuals, which may indicate a lack of dependence of PAP on NREM and REM sleep stage [11].

Excessive rises in PAP and SDB may be mutually linked by either direct effects or via comorbid conditions (Fig. 1). Thus, hypoxemia during sleep due to hypoventilation or apneas/hypopneas may induce PH through hypoxic and/or hypercapnic pulmonary vasoconstriction and sympathetic activation as detailed below. Conversely, it has been suggested that precapillary PH associated with right ventricular failure may promote instability of ventilatory control leading to sleep apnea through similar mechanisms as in left ventricular failure with CSR/CSA [12]. Furthermore, patients suffering from SDB in association with other conditions predisposing to an elevated PAP such as chronic lung disease, in particular chronic obstructive pulmonary disease (COPD), chronic alveolar hypoventilation related to chest wall deformities or neuromuscular disease with respiratory muscle weakness, may be susceptible to developing precapillary PH. According to epidemiologic studies in overweight patients, both hypoxia and hypercapnia are associated with precapillary PH, although their relative significance has not been conclusively assessed [13]. Thus, in one study in obese patients with PH [14], $PaCO_2$ was correlated with PAP; 3 months of treatment with noninvasive ventilation reduced both $PaCO_2$ and PAP. Since PaO_2 was also improved, the independent effect of hypercapnia could not be assessed. Nevertheless, other studies in preparations of pulmonary arteries [15], animal models [16, 17] and healthy volunteers [18, 19] have suggested an independent effect of hypercapnia inducing PH by pulmonary vasoconstriction through an NO-mediated pathway and by enhanced vasoreactivity of pulmonary arteries. Thus, intermittent sleep-related hypoxemia and hypercapnia alone or in combination with chronic hypoxemia and structural alterations of the lung may predispose to precapillary PH, right ventricular dysfunction and failure. The paucity of conclusive data on this topic may be due to the complexity of measuring pressure and flow in the pulmonary circulation by right heart catheter. Novel echocardiographic and magnetic resonance imaging and other techniques may provide further insights into these interactions in the future [20, 21]. Various pathophysiologic mechanisms linking PH and SDB will be discussed in the following.

OSA and Precapillary PH

Patients with OSA may show acute or chronic hemodynamic changes associated with intermittent hypoxemia. Various pathophysiologic mechanisms have been discussed. Comorbid conditions additionally play an important role.

Fig. 2. Example of polysomnographic recording during phasic and tonic rapid eye movement (REM) sleep. There are major rises in both systemic and pulmonary artery pressure (arrows) during apneas in phasic REM sleep (adapted from Niijima et al. [10]). Abdo., abdomen; HR, heart rate; PAP, pulmonary artery pressure; Psa, systemic arterial pressure.

Hypoxic and Hypercapnic Pulmonary Vasoconstriction. Hypoxic pulmonary vasoconstriction is an important mechanism that contributes to maintaining an adequate ventilation-perfusion relationship (V/Q) in the lungs [22]. Thus, reducing ventilation in a part of the lungs leads to regional hypoxia with vasoconstriction that reduces shunt perfusion. Motley and Cournand [23] showed that breathing a hypoxic gas mixture containing 10% oxygen induced a rise in PAP. Persistent pulmonary vasoconstriction due to hypoxia may result in vascular remodeling and thus chronic precapillary PH. As outlined above, hypercapnia may also promote pulmonary vasoconstriction in conjunction with or independent of hypoxia. Both hypoxia and hypercapnia are therefore considered to be responsible for the development of precapillary PH in chronic hypoventilation due to obesity or lung diseases [24]. Some animal studies have suggested that nocturnal intermittent hypoxia in OSA is sufficient to cause persistent daytime PH und right ventricular dysfunction [25] but this is debated in the case of human OSA. Some studies on this topic included patients with coexisting conditions such as COPD or obesity resulting in sustained hypoxemia by ventilation-perfusion mismatch, diffusion impairment or hypoventilation [26–30], others were performed in sleep apnea patients without comorbidities [31–33]. It is conceivable that patients with chronic lung disease such as COPD that may cause hypoxemia and a reduced pulmonary vascular bed, or patients with hypoxemia due to obesity associated with hypoventilation may be at particular risk to develop pulmo-

nary vascular remodeling and persistent elevations in PAP in the presence of aggravated hypoxemia during sleep by OSA.

Sympathetic Overstimulation. In patients with OSA, breathing efforts against an occluded airway cause large fluctuations in systemic blood pressure associated with hypoxemia, arousals and surges of sympathetic tone [34]. Moreover, major rises in both systemic and PAP during long apneas in phasic REM sleep have been described (Fig. 2) [10]. The large arterial pressure swings associated with sympathetic overstimulation in OSA patients induce vascular shear stress and promote endothelial dysfunction [35–37]. Repetitive hypoxia and reoxygenation may upregulate hypoxia-inducible factors, vascular endothelial growth factor and erythropoietin, and trigger inflammatory processes [38]. These mechanisms may lead to elevations in PAP that persist even during daytime and over prolonged time as suggested for the pathophysiology of systemic hypertension in OSA.

Increased Inspiratory Effort. In OSA, the increased inspiratory effort against an occluded airway causes large intrathoracic pressure swings that create mechanical stress on the aorta and the left ventricle and increase afterload contributing to the development of systemic hypertension and cardiovascular disease in affected patients. Acute right ventricular enlargement because of increased venous return may impair left ventricular filling. Together, these mechanisms may lead to an increased pulmonary venous pressure, and postcapillary PH [39]. Conceivably, similar mechanisms might also lead to elevated PAP. Negative intrathoracic pressure during OSA might additionally cause PAP to rise by increased pulmonary vascular resistance [40]. A similar mechanism has recently been documented in patients with COPD experiencing major increases in pleural pressure swings during exercise that were accompanied by rises in PAP [41].

Precapillary PH and Ventilatory Instability

Several studies have shown that severe precapillary PH associated with right ventricular failure and low cardiac output may be associated with SDB including CSR/CSA as well as OSA, similar to what is observed in patients with severe left ventricular failure and postcapillary PH [7, 42, 43]. The mechanisms responsible for the destabilizing effect of PH on control of breathing remain elusive. However, factors that predispose to CSR/CSA in left ventricular failure may also be relevant in right ventricular failure. For example, increased chemosensitivity associated with sympathetic stimulation may promote an overshooting ventilatory response to apneas/hypopneas. Moreover, an excessive circulatory delay due to a reduced cardiac output in severe precapillary PH may prolong the time required to transport oxygenated blood from the lungs to the chemoreceptors so that the feedback to the respiratory center is desynchronized [8, 44, 45]. Patients with precapillary PH, especially those with right ventricular heart failure and fluid overload, may possibly exhibit nocturnal breathing instability through rostral fluid redistribution at night as suggested by studies in patients with systemic hypertension [46].

Prevalence and Importance of PH in SDB

There is increasing evidence of an association of SBD with systemic hypertension, incidence of stroke, heart failure, myocardial infarction, arrhythmias and sudden cardiac death [47–49]. Similar data on potentially adverse effects of SDB in patients with PH are not available. A research of the literature on the prevalence of precapillary PH in patients with SDB unselected for the absence of comorbidities as well as in patients with concomitant lung and heart diseases has identified the studies summarized in Table 1.

In observational case studies of OSA patients unselected for absence of comorbidities (Table 1, upper part), the prevalence of PH has varied largely between 17 and 60% [27, 50]. When studies excluded patients with coexisting lung and heart diseases, the prevalence of OSA-related PH was estimated at up to 40% (Table 1, lower part) [31, 32, 50–52]; however, in only 2 of these studies [31, 51] was the current definition of PH (mean PAP >25 mm Hg) applied. The wide range of prevalence rates may be due to differences in patient selection, disease definition and methodological differences, i.e., invasive pressure measurement with right heart catheter versus Doppler echocardiography. The value and limitations of Doppler echocardiography in the evaluation of PH patients have been addressed in the recent ESC/ERS guidelines [53]. Additionally, using PAP cutoff values for defining the presence of PH that are different than the current one (mean PAP ≥25 mm Hg) might have confounded the prevalence rates. Data from appropriately powered epidemiologic studies using right heart catheter data and the current definition of PH are not available to date.

In a large sample of 220 patients with OSA [27], 17% revealed a mean PAP of >20 mm Hg (i.e., this study used a cutoff for defining PH that was lower than the mean PAP ≥25 mm Hg required for the diagnosis of PH according to current standards). Some of these patients

Table 1. Pulmonary artery pressure in patients with sleep-disordered breathing

First author [Ref.], year	Topic	Design	Participants	Outcome	Remarks
Patients with obstructive sleep apnea (mixed group of patients with and without coexistent lung disease)					
Fletcher [50], 1987	precapillary PH in OSA with lung disease	case series	among 24 patients with OSA, 19 had coexisting lung disease, 5 had no coexisting lung disease	in 15 of 24 patients, right heart catheter data were available; mPAP was >25 mm Hg in 9 of these 15 patients (in 7 with and 2 without coexistent lung disease)	
Weitzenblum [30], 1988	precapillary PH in OSA with and without lung disease	case series	46 with OSA; no overt COPD	9 of 46 patients had mPAP >20; these had lower PaO_2, FEV_1, FVC, higher $PaCO_2$, but similar AHI than those with lower mPAP; predictors of PH: pO_2, pCO_2 FEV_1, FEV_1/FVC	precapillary PH was not correlated with AHI
Krieger [29], 1989	precapillary PH in OSA with lung disease	case series	100 with OSA; AHI >5/h	19/100 OSA patients had mPAP >20 mm Hg; they had lower pO_2, higher pCO_2, and higher AHI than those with lower mPAP; predictors of PH: FEV_1, pO_2, pCO_2	
Laks [13], 1995	precapillary PH in OSA with and without lung disease	case series	100 with OSA (AHI >20/h; oxygen desaturations >4%)	42/100 OSA patients had mPAP >20 mm Hg; of these 6 with normal pO_2, pCO_2 36–65 mm Hg; predictors of PH: pO_2, (pCO_2) FEV_1	FEV_1 %pred. not given; incomplete multivariate regression (BMI not evaluated). 6 patients with OSA and precapillary PH but normal PaO_2
Chaouat [26], 1995	COPD in OSA	case series	265 with OSA AHI >20/h of these 30 with coexistent COPD FEV_1/FVC ≤60%	OSA/COPD overlap in 30/265 (11%); these patients had reduced lung function (obstructive pattern, FEV_1/FVC ≤60%), were male, had similar BMI, lower SaO_2, impaired arterial blood gases, and a higher mean mPAP of 20 mm Hg compared to OSA patients without COPD (mean mPAP 15 mm Hg); predictors of mPAP: $PaCO_2$, FEV_1, airway resistance, SaO_2	
Chaouat [27], 1996	precapillary PH in OSA with and without lung disease	case series	220 with OSA AHI >20	37/220 had mPAP >20 mm Hg; 16/220 had mPAP >25 mm Hg; OSA patients with mPAP >20 had lower PaO_2, nocturnal SaO_2,FEV_1, FEV_1/FVC, higher AHI, $PaCO_2$ predictors of PH: $PaCO_2$, FEV_1, mean nocturnal SpO_2	precapillary PH in OSA is linked to COPD, hypoxemia, hypercapnia
Sanner [33, 63], 1997	precapillary and postcapillary PH in OSA without lung disease	Case series	92 with OSA and no evidence of lung disease AHI >10/h	18/92 had mPAP >20 mm Hg, 8 of these had also PCWP >13 mm Hg	there is a possible overlap of patients [33, 62]

Table 1 (continued)

First author [Ref.], year	Topic	Design	Participants	Outcome	Remarks
Patients with obstructive sleep apnea without coexistent lung or heart disease					
Fletcher [50], 1987	precapillary PH in OSA without lung disease	case series	among 24 patients with OSA, 5 had no coexisting lung disease	2 of 5 patients had a slightly elevated mPAP of 26 and 27.7 mm Hg	
Sajkov [51], 1994	precapillary PH in OSA without lung disease	case series	27 patients with OSA, AHI >10/h, no lung or heart disease	11/27 patients had mPAP >20 (range 20–26) mm Hg; predictor of mPAP was PaO_2 only, not pulmonary function or BMI or AHI	some OSA patients responded excessively to hypoxia suggesting remodeling of pulmonary vasculature; the cutoff for PH in this study was 20 mm Hg (not ≥25)
Sajkov [52], 1999	precapillary PH in OSA without lung disease	case series	32 with OSA with AHI >10/h and PFT >80% pred., no cardiac disease	11/32 OSA patients had mPAP >20 mm Hg (range 20–31); no difference in pulmonary function or BMI between groups; isocapnic hypoxia with SpO_2 80% induced a greater rise in mPAP in those with mPAP >20 mm Hg at baseline; hyperoxia reduced mPAP more in patients with mPAP <20 mm Hg at baseline; dobutamin infusion increased mPAP more in patients with mPAP >20 mm Hg at baseline than in remaining patients; mPAP was correlated with airway closure during tidal breathing	some OSA with normal lung function and no cardiac disease may have mild precapillary PH; the cutoff for PH in this study was 20 mm Hg (not ≥25 mm Hg)
Bady [32], 2000	precapillary PH in OSA without lung disease	case series	44 with OSA (AHI >5/h), normal pulmonary function (FEV_1 >70%, FEV_1/FVC >60%)	mPAP >20 mm Hg, PCWP <15 mm Hg in 12/44 OSA patients without lung disease; AHI in OSA with and without mPAP >20 mm Hg was not different; predictors of mPAP: PaO_2, $PaCO_2$, nocturnal SpO_2, higher BMI	no patients with lung disease. mPAP related to BMI and pO_2, not AHI; the cutoff for PH in this study was 20 mm Hg (not ≥25 mm Hg)
Alchanatis [31], 2001	precapillary PH in OSAS, effect of CPAP	case control study, before after CPAP	29 OSA patients with AHI >15/h: in 19 of these right heart catheter data were shown	3/19 of OSA patients had mPAP ≥25 mm Hg; mPAP was correlated with age, PaO_2, BMI	

Several studies used definitions of precapillary pulmonary hypertension (PH) that are not consistent with the current definition of mPAP ≥25 mm Hg and PCWP <15 mm Hg, the criteria for PH are indicated for individual studies. OSA, obstructive sleep apnea; COPD, chronic obstructive pulmonary disease; mPAP, mean pulmonary artery pressure; AHI, apnea/hypopnea index; BMI, body mass index; CTEPH, chronic thromboembolic pulmonary hypertension; CSR, Cheyne-Stokes respiration; PFT, pulmonary function testing; SDB, sleep-disordered breathing; CPAP, nocturnal continuous positive airway pressure treatment; PCWP, pulmonary capillary wedge pressure.

seem to have suffered from COPD. Laks et al. [13] studied a heterogeneous group of 100 patients with OSA. The mean daytime PAP was 21 mm Hg and the apnea/hypopnea index (AHI) varied between 20 and 100 events/h. Forty-two patients had a mean PAP >20 mm Hg (a definition of PH different from current standards). Several patients were hypoxemic and hypercapnic during daytime and some had impaired pulmonary function suggesting coexisting COPD. In addition, some patients were very obese; PaO_2, $PaCO_2$ and FEV_1 explained 33% of the variation in PAP suggesting that the high prevalence of precapillary PH of 42% in this cohort may have been re-

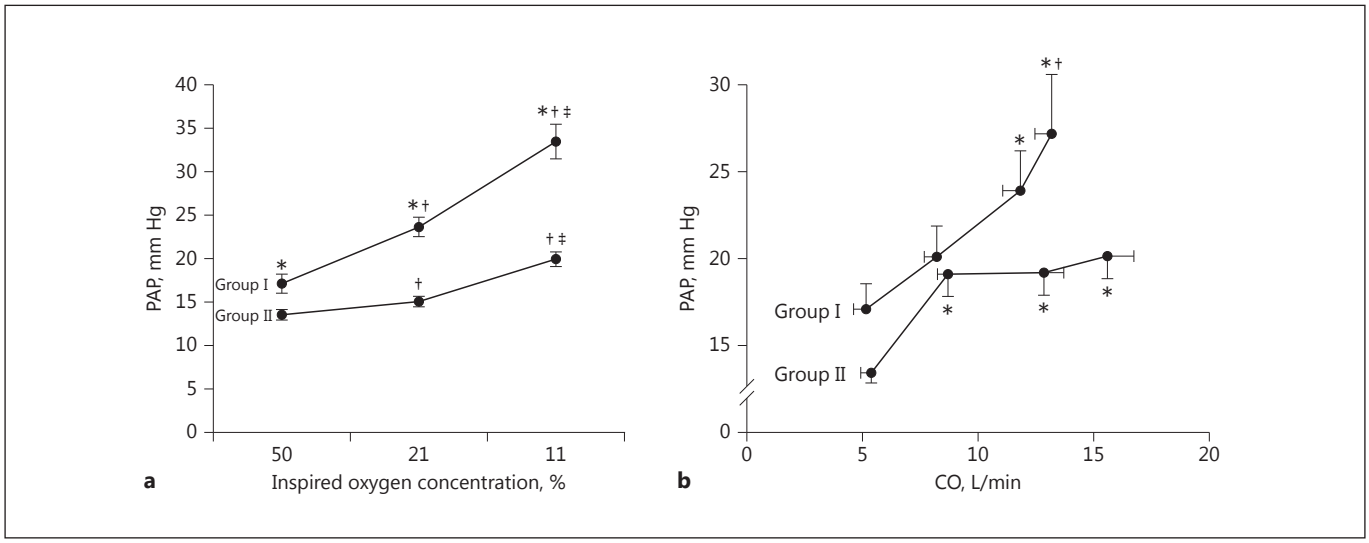

Fig. 3. a Evaluation of hypoxic pulmonary vasoreactivity by exposing patients with obstructive sleep apnea to an FiO_2 of 11, 21 and 50%. Patients with a mean pulmonary artery pressure (PAP) of >20 mm Hg at baseline on room air had a brisker response to changes in FiO_2 than patients with a mean pulmonary artery pressure ≤20 mm Hg suggesting an exaggerated hypoxic response of the pulmonary vasculature of patients with initially higher pulmonary artery pressures. **b** During a dobutamin challenge test that increased cardiac output (CO) pulmonary artery pressure increased to higher values in patients with a mean pulmonary artery pressure of >20 mm Hg at baseline compared to the rest of the patients in whom PAP reached a plateau at values of less than 20 mm Hg (adapted from Sajkov et al. [52]). * $p < 0.05$ vs. group II (PAP ≤20), † $p < 0.05$ vs. FiO_2 50%, ‡ $p < 0.05$ vs. FiO_2 21%.

lated to coexistent disorders and to the liberal PH definition of mean PAP >20 mm Hg at that time.

Sajkov et al. [51] compared a group of OSA patients with mildly elevated PAP still within the normal range (mean PAP of 22.8 mm Hg) with another group of patients with a similar degree of OSA but low normal PAP (mean PAP of 14.6 mm Hg). In both groups, no heart or lung disease could be found even by detailed examinations, but the patients with higher PAP had lower PaO_2. The authors speculated that these patients had an excessive hypoxic response of the pulmonary vasculature that promoted the development of PH in combination with OSA.

To further corroborate the mechanisms involved in the rise of PAP in certain patients with OSA, Sajkov et al. [52] studied 32 OSA patients without any evidence of cardiac or pulmonary disease. Eleven of them had a mean PAP >20 mm Hg but a similar AHI, body mass index and daytime arterial blood gas values as the remainder of the patients with a mean PAP <20 mm Hg. Although both groups of OSA patients had normal spirometry, the patients with higher mean PAP had a reduced closing volume measured by the nitrogen washout technique. The difference between functional residual capacity and closing volume was negative indicating that some patients experienced intermittent closure of peripheral airways during tidal breathing. This might have predisposed them to a V/Q mismatch and hypoxemia thereby contributing to elevated PAP. In the same group of OSA patients, Sajkov et al. [52] evaluated the hypoxic pulmonary vasoreactivity by exposing patients to an inspiratory fraction of oxygen (FiO_2) of 11, 21 and 50% while PAP was monitored. Patients with elevated PAP at baseline on room air above 20 mm Hg had a brisker response to changes in FiO_2 than patients with lower baseline mean PAP. In addition, challenges with dobutamin infusion were performed. With increases in cardiac output, PAP rose significantly more in patients with mean PAP >20 mm Hg at baseline compared to the rest of the patients. These findings were considered to be consistent with vascular remodeling in some of the OSA patients [52] (Fig. 3).

SDB in Patients with Precapillary PH

So far, the direct or indirect effects of SDB on precapillary PH had been discussed. There is evidence that the relation may also act in the opposite direction, so that precapillary PH may trigger SDB (Fig. 1). As many features of patients with left ventricular failure and SDB,

Table 2. Sleep-disordered breathing among patients with precapillary pulmonary hypertension

First author [Ref.], year	Topic	Design	Participants	Outcome	Remarks
Rafanan [56], 2001	Nocturnal hypoxemia in precapillary PH	case series	13 with PAH	10/13 were nocturnal desaturators, i.e., >10% of nighttime with SpO_2 <90%; desaturators had lower FEV_1 and PaO_2, higher hemoglobin concentration	
Schulz [54], 2002	CSR in precapillary PH	case series	20 with PAH	CSR in 6/20 who had more severe precapillary PH; nasal oxygen eliminated CSR	suggests effect of oxygen
Schulz [64], 2004	CSR in precapillary PH	case report	1 female with PAH	polysomnography before and after lung transplantation shows disappearance of CSR	
Minai [55], 2007	nocturnal hypoxemia in precapillary PH	case series	43 with PAH	30/43 were desaturators with >10% of the night-time with SpO_2 <90%; desaturators had higher hemoglobin, higher brain natriuretic peptide, higher mPAP, lower cardiac index	
Ulrich [7], 2008	SDB in precapillary PH	case series	38 with precapillary PH (PAH 23, CTEPH 15)	17/38 had AHI >10/h; 4 had OSA; sleep-disordered breathing was associated with reduced quality of life	
Prisco [43], 2011	SDB in precapillary PH	case series	28 with precapillary PH (PAH 9, associated PH 21	precapillary PH severity best correlated with combination of AHI and time of the night spent with SpO_2 <90%	
Hildenbrand [65], 2012	nocturnal hypoxemia in PAH, CTEPH	case series	63 with precapillary PH (44 PAH, 19 CTEPH)	77% spent >10% of the nighttime with SpO_2 <90%	
Jilwan [42], 2013	SDB in PAH, CTEPH	case series	46 with precapillary PH (29 PAH, 17 CTEPH)	89% had sleep apnea, 83% had nighttime hypoxemia	BMI <35 FEV_1 >60%
Dumitrascu [66], 2013	SDB in various forms of precapillary PH	case series	169 with precapillary PH (28 PAH, 51 CTEPH, 16 collagen vascular disease, 59 chronic lung disease, 15 other)	26.6% had sleep apnea, AHI >10/h, of these 16.0 % had OSA, 10.6% had CSA	

PH, pulmonary hypertension; PAH, pulmonary arterial hypertension; CSR, Cheyne-Stokes respiration; CTEPH, chronic thromboembolic pulmonary hypertension; mPAP, mean pulmonary artery pressure; SDB, sleep disordered breathing; OSA, obstructive sleep apnea; AHI, apnea/hypopnea index; BMI, body mass index

such as low cardiac output, increased sympathetic tone, and arrhythmia, are also common in patients with precapillary PH and right ventricular failure, some authors have also looked at SDB in patients with precapillary PH of different origins. These studies are summarized in Table 2.

Schulz et al. [54] were the first to describe CSR/CSA in patients with pulmonary arterial hypertension (PAH; WHO class I). Patients had typical periodic breathing with waxing and waning of ventilation. Fourteen had an AHI of <20/h and 6 had an AHI >20/h with nearly exclusively central events consistent with CSR/CSA. In order to further evaluate the prevalence and type of sleep-related breathing disturbances in PH patients, we performed a prospective study in consecutive patients with either PAH or chronic thromboembolic pulmonary hypertension [7]. In none of these patients had SDB been suspected on clinical grounds and most of them had been treated for PAH/chronic thromboembolic pulmonary hypertension with various drugs for several months or years. A total of 38 patients were studied. In Figure 4, the total AHI in each patient and the relation between central and obstructive events are shown. Eighteen patients or 47% had an elevated AHI of >10/h. The large majority had pre-

dominant CSR but 4 patients also had more than 10 obstructive events per hour. No significant differences in hemodynamics, arterial blood gases or pulmonary function between the groups with and without increased AHI were found. Polysomnography and pulse oximetry were used to assess SDB in the study by Ulrich et al. [7] to evaluate the diagnostic accuracy of the simple technique in this setting. Although pulse oximetry had been proposed as part of the routine evaluation of patients with PH to detect nighttime hypoxemia [55], oximetry alone revealed a poor diagnostic performance (area under the receiver operating characteristic curve of only 0.66 ± 0.14) in identifying patients with an AHI ≥10, when compared with polysomnography [7]. Thus, pulse oximetry alone cannot be recommended as diagnostic tool for SDB in PH patients. Whereas in some studies on the association of precapillary PH with SDB nocturnal hypoxemia without sleep apnea was the predominant finding [55, 56], others found sleep apnea without severe persistent hypoxemia [7, 54] or a combination of both persistent hypoxemia and sleep apnea [42, 43]. In a most recent study in Kyrgyz highlanders, a high prevalence of mainly OSAs was found among individuals with high-altitude PH, a particular form of precapillary PH occurring in life-long residents at altitudes >2,500 m. This observation suggests that individuals exposed to the combined stimuli of chronic hypoxemia due to high-altitude residence and intermittent nocturnal hypoxemia due to sleep apnea may be more susceptible to PH compared to highlanders without sleep apnea [57].

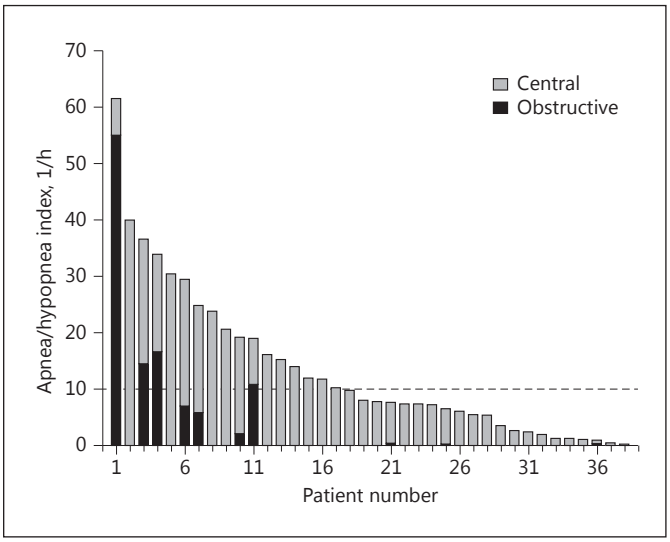

Fig. 4. Apnea/hypopnea index in 38 patients with precapillary pulmonary hypertension. The bars are ordered in descending order of the total apnea/hypopnea index with the black part representing the obstructive and the gray part the central events. A value of ≥10 was observed in 45% of patients, the median value was 8/h (reproduced from Ulrich et al. [7]).

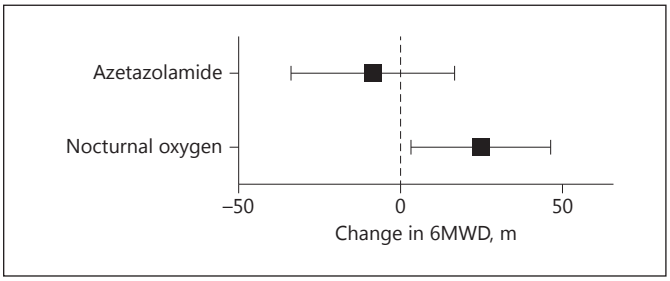

Fig. 5. Results of a randomized, placebo-controlled double-blind trial evaluating the effect of 1 week of nocturnal oxygen therapy and acetazolamide, respectively, on the 6-min walk distance (6MWD) in patients with precapillary pulmonary hypertension and sleep-related breathing disturbances. Mean differences and 95% confidence intervals of the 6-min walk distance between acetazolamide and placebo and between oxygen and sham oxygen (ambient air) are shown (reproduced from Ulrich et al. [62]).

Treatment of PH in SBD

Tracheostomy and supplemental oxygen have been shown to reduce PAP in patients with COPD and nighttime hypoxemia [58] but this intervention (tracheostomy) is rarely performed nowadays. Limited data on effects of continuous positive airway pressure (CPAP) treatment in patients with OSA on PAP are available. In a case-control study by Alchanatis et al. [31], 29 patients without evidence of pulmonary or cardiac disease were studied with Doppler echocardiography before and after 6 months of CPAP treatment. Of these 29 patients, 6 had mild precapillary PH. The control group consisted of 12 healthy subjects. Older subjects and those with increased body mass index in the OSA group were more prone to suffer from (generally mild) precapillary PH and 6 months of CPAP caused a significant fall in PAP in hyper- and normotensive patients pointing to OSA as an independent risk factor for the development of precapillary PH. In another study including patients with moderate to severe OSA, 4 months of CPAP significantly reduced the PAP, especially when the PAP was elevated at baseline [59]. Moreover, the pulmonary vascular response to hypoxia decreased after CPAP treatment [59]. In a randomized crossover trial in patients with OSA using sham or effective CPAP for 12

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Table 3. Interventional studies in patients with precapillary pulmonary hypertension and sleep apnea

First author [Ref.], year	Topic	Design	Participants	Outcome	Remarks
Alchanatis [31], 2001	precapillary PH in OSAS, effect of CPAP	case control study, before after CPAP	33 with OSA AHI >15/h: 29 with OSA at baseline and after CPAP, 12 snorers	OSA patients had higher mPAP than controls; 3/19 OSA had mPAP >25 mm Hg; mPAP was correlated with age, PaO_2, BMI. CPAP reduced mPAP in all OSA patients (see also Table 1)	baseline assessment by right heart catheterization, follow-up assessment of PAP by echocardiography
Sajkov [59], 2002	precapillary PH in OSAS, effect of CPAP	observational study on CPAP effect on precapillary PH in OSA without lung disease	20 with OSA of 32 OSA with AHI >10 and pulmonary function variables >80 % predicted, no cardiac disease	5/20 OSA had mPAP >20 mm Hg; sPAP was reduced in all patients after 4 months of CPAP except in 1 non-compliant patient; hypoxic vasoreactivity was reduced and flow response was shifted downward in a parallel fashion; systemic blood pressure was also reduced	results may suggest that PAP was reduced because of improved endothelial function and possibly reverse remodeling in some patients.
Arias [60], 2006	precapillary PH in OSAS and CPAP	randomized sham control crossover, 2 × 12 weeks	23 OSA, 10 controls	sPAP reduction by 5 mm Hg, sPAP in OSA >controls	OSA induces precapillary PH
Colish [67], 2012	precapillary PH in OSA and CPAP	observational, prospective study on one-year treatment effects	47 OSA, AHI 63±30/h	s PAP decreased significantly from 54 to 39 mm Hg	
Ulrich [62], 2015	precapillary PH and SBD; effect of nocturnal oxygen vs. placebo and vs. acetazolamide	randomized, double-blind double crossover	23 patients, with precapillary PH; 16 PAH, 7 CTEPH	oxygen improved 6-min walk distance after 1 week of treatment, acetazolamide had no significant effect compared to placebo. Both oxygen and acetazolamide improved the AHI and nocturnal oxygenation; sPAP did not change with any of the treatments	nocturnal oxygen therapy also improved nocturnal oxygenation, periodic breathing, functional class and indices right ventricular function
Marvisi [68], 2015	precapillary PH in OSA, effect of CPAP and UPPP	observational case study, before and after CPAP or UPPP	25 of 75 with OSA and elevated mPAP	17 treated with CPAP, 8 with upper airway surgery, sPAP reduction from mean 40 to 25 mm Hg (CPAP) and 22 mm Hg (surgery), n.s. between groups	CPAP and UPPP cohort differed largely in BMI at baseline

PH, pulmonary hypertension; OSA(S), obstructive sleep apnea (syndrome); CPAP, continuous positive airway pressure; AHI, apnea/hypopnea index; mPAP, sPAP, mean and systolic pulmonary artery pressure estimated by echocardiography; BMI, body mass index; BP, blood pressure; CTEPH, chronic thromboembolic pulmonary hypertension; PAH, pulmonary arterial hypertension; SDB, sleep disordered breathing; UPPP, uvulopalatopharyngoplasty.

weeks, PAP was reduced significantly by CPAP [60]. The studies mentioned above have not included right heart catheter data to demonstrate whether improvement in pulmonary hemodynamics occurred because of improvement in precapillary PH or by improving left ventricular function.

Supplemental nocturnal oxygen has been used in patients with nocturnal hypoxemia-related PH. In COPD patients, long-term home oxygen therapy did not improve survival in patients with mild to moderate hypoxemia or in those with arterial desaturation at night only [61]. It is uncertain whether this also applies to PH pa-

tients with nighttime hypoxemia and SBD. In the only randomized, placebo-controlled study in patients with precapillary PH and SDB nocturnal oxygen therapy improved the 6-min walk distance already after 1 week (Fig. 5) and reduced the AHI [62]. In turn, acetazolamide (2 × 250 mg tablets/day) reduced the AHI to a similar degree but did not change the 6-min walk distance [62]. Whether selected patients with PAH and SDB may benefit from specific PH therapy has not been studied. Table 3 gives an overview of interventional studies with CPAP or oxygen in patients with SBD associated precapillary PH.

Conclusions

Available data suggest that about one half of patients with OSA unselected for the absence of comorbidities have intermittent or sustained elevations of the PAP and that up to one half of patients with precapillary PH suffer from SBD. Several pathophysiologic mechanisms predispose patients with SBD to precapillary PH. However, precapillary PH in OSA not associated with any other conditions leading to hypoxemia seems to be rare. Optimized therapy of any comorbidity such as COPD and obesity seems to be crucial. For the remaining patients with both SDB and PH but without comorbidity, positive pressure ventilation or oxygen might be beneficial in terms of lowering the PAP but this has not been evaluated in rigorous randomized trials. In patients with precapillary PH associated with SDB nocturnal oxygen supplementation has improved exercise performance and SDB in one trial [62] but long-term studies that confirm these findings are lacking. The role of CPAP or other modes of positive pressure ventilation and of PH specific drugs in the treatment of patients with precapillary PH and central or OSA requires further evaluation in randomized trials.

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